

AGCAGAGAGCCTGGTGGCATGGACATCTTATCCACATACCTTAGTGTGAC
 CACGCCGACAGAAAACTACTAAGGCCATCTCAGGGTGCCTGTGCCAGGAGA
 GGGGGCGGTGCCCCGGGCCAGAGCCATGCCCTCGGCCTGAAGCTCCG
 CAGGACTCGGCCTACAACGTCTGAGCAAGAACTGCTTGTGCCGGATC
 CGCCTGCTGGACAGCAATGTCATCGAGTGCACGCTGTCGGTGGAAAGCACGG
 GGCAAGAGTGCTGGAGGCCGTGGCCCCAGAGGCTGGAGCTGAGGGAGACGC
 ACTACTCGGCCTTGGTTCTCAGCAAGAGCCAGCAGCGAGATGGGTAGA
 GCTGGAGAACGCCACTGAAGAAACATCTGGACAAGTTGCTAACGAGCCTCTG
 CTTTCTCGGAGTCATGTTCTATGTGCCAAATGTGTACGGCTTCAGCAGGA
 GCCACAAGATATCAGTATTACCTGCAAGTCAAAAAAGACGTGCTTGAAGGA
 CGGTTGCGGTGCTCCCTGGAACAAGTGTACCGGCTGGCTGGCTAGCTGTG
 AAGCTGACTTCGGAGATTATAACCAGTTGATTCCAAGAGTTCCCTCCGAGA
 GTATGTGCTCTTCCTATGGATTGGCATGGAGGAGGCGGCTGGAGGAG
 CTAACCCAGAAGGTGGCCCAGGAACACAAAGCTCATAGCGGGATCCTGCCG
 GCTGAAGCTGAACGTACATCAACGAGGTAGAGCGTTGGATGGATTG
 GACAGGAGATCTCCCCGTGAAGGACAGTCATGGCAACAGCGTGCACCTCGG
 CATCTTCTCATGGGGATTTGTGAGGAACAGGGTCGGGAGACAGGCAGTG
 ATATACAGGTGGAATGACATTGGAGTGTACTCACAGCAAAGCAGCCATCC
 TGTTGGAGCTGATTGACAAGGAGGAGACCGCGCTTCCATACAGATGATAT
 TGAAAATGCCAAGTACATTCTGGTTGTTACCACTCGGCACAAATTACA
 AACAGAACAAAGATCTGCACTGAACAGTCAAATTCTCCACCCCCAATCAGACG
 CCAGCCCACCTGGAGCCGGTCCTCACTGCCAAGGCAGCAGCCGTATATCTG
 CCTCCCATGCATGTCCAGTGCAGTGACTACTCGGAGACCCATACTCCCA
 AGACAGCATTTCGGGAACGAAGAACGCTTGTACTGCCGTCTCACAAAC
 AGCCTGGACCTTAATTACTGAAACGGCACCGTCACCAATGGCAGCGTGTGCA
 GCGTTCACAGCGTCAACTCCCTCAGCTGCTCCAGAGCTTCATTCAAGCGTCT
 CCAGTGTCTCCAACCTAGCATCCCTGGAGTGCACATCATGAGGGCCGATT
 ACATCCCCAGCCACCGCCACAGCACCATCATGTGCCGTCTACAGGCCGAC
 CCCAGATTACGAGACGGTCATGAGGCAGATGAAGAGGGGTCTGATGCACGC
 AGACAGCCAGAGCCGGTCTCGCTAACCTCAATATCATCAACACCCATGCC
 TATAACCAGCCGAGGAACGGTACAGCCAGCCGGAGATGCCGGAGAGG
 CATCCCTACACGGTCCCTATGCACACCAGGGTGCACGGTCACAAACTTG
 TAAGTCCGTCTGACCAGATGAACCCCCAAATTGTGCGATGCCATCAAGCC
 AGGGGCCAGTCCATCTCACACAGTGCAGCACTCCAGAACAGCCACATG
 CAGCTCCAAGGAGCACAACACTATAGCACAGCCCACATGCTCAAGAACATC
 TATTCAAGGCCACCCCCCTACCCCTCGGCCGGTCTGCCACAGCACCCCA
 GACCTCGCCAGCCACCGCCACAAGTACGTCAAGCGCAGGCCGTGATCTGG
 TAACTCGGAAGGTGCAGCTCTCGTAAAGACCTCCAGGAGGACAGCTCACC
 TGTGGTCCATCAGTCTGCAGGAGGTGAGCGAACCCCTCACAGCCACCAAG
 CACCATGGCGGCGGCGGTGGCACGGTGAATAACGCCACAGCCTGGAGGTG

FIGURE 1A

ATGAACAGCATGGT GAGAGGCATGGAGGCCATGACACTGAAGTCACTCAATA
 TCCCCATGGCTCGCCGCAACACCCCTCGGGAGCAGGGCCCTCCGAGGAGAC
 GGGCGGCCACGAAGTGCACGGTCTCCCCAGTATCACCAACAAGAACATTC
 TCGGATGCCACCCTGCTGATCCACAGCAGTGAGAGCGAGGAAGAGGAGGAG
 ACCCTGGAGGCTGCACCTCAGGTTCTGTGCTTCGAGAGAAAGTAGAATACA
 GTGCCCAGCTGCAGGCTGCCCTGGCCCGATCCCCAACAGGCCCCCACCTGA
 GTACCCAGGGCCAAGAAAAAGTGTCAAGTGGGCAGTGAGACAGGACCA
 GGGAACCCCTCTCCTGCCATGCCAGGTGCAGGGTGTGAGACACGGACCA
 TCCAAGGCCCTCAGTGTCTCCCGGGCAGAGCAGCTGGCTGTCAACGGTGCCT
 CTCTGGGTCCCTCCATCTGAGCCTGACCTAACCAAGCGTGAAGGAGCAGGGT
 CAAGAAAGAGCCTGTGAAGGAAAGGCCGGTGTCAAGAGATGTTCTCCCTGGAG
 GACAGCATTATAGAGAGAGAGATGATGATCAGGAATCTAGAGAACAGAACAG
 ATGACGGGCCCGCAGGCACAGAACAGAGACCGCTGATGTTGGCAGCGCTGAAT
 GGGCTCTCGGTGGCCCGAGTGTGGGGGGAGATGGTCGCCATGATGCCA
 CCCGAGTCCCCATAGACGAGAGGCTCAGAGCCCTGAAGAACAGCTGGAAAG
 ATGGAATGGTGTTCACAGAATATGAGCAGATTCAAACAAAAAGGCCAACG
 GCGTCTTCAGCACCGCCACTCTGCCCTGAGAACGCCAGCGCAGCCGGATCCG
 AGAAGTTGTCCCATTAGAGGAGAACATCGAGTGGAGCTCATCCGACCAAAGAA
 AACAAACACAGGCTATATCAACGCCCTCACATCAAGGTGGTGGCGCGGAT
 CAGAATGGCACTACATGCCACCCAGGGGCCCTGCCACATACGTGCCATGA
 CTTCTGGCAGATGGTGTGGAGCAGGGGGTGAATGTGATGCCATGGTCACT
 GCAGAGGAGGAGGGTGGACGGACAAAAGCCATCGATACTGGCCCAAACCTG
 GGGTCCAAGCATAGTTCTGCCACCTACGGCAAGTTCAAGGTACCACAAAGT
 TCCGGACAGATTCTGGTGCTATGCAACGACGGCCTAAAGGTGAAGCACCT
 GCTGTCCGGCAGGAGAGGACCGTGTGGCACTTGCAGTACACGGACTGGCCC
 CACCACGGCTGCCAGAACAGCTCAAGGATTGGTCTACTTGGAGGAAA
 TCCAGTCAGTCCGACGCCACACCAACAGCGTGTGGAAAGGCATCAGGACCAAG
 GCACCCCCCCCATCGTGGTCACTGCAGCGCGGTGTGGAAAGGACTGGTGTG
 GTTATCCTCTGTGAGCTCATGATCTACTGCCCTGGAACACAACGAAAAGGTGG
 AGGTGCCACGATGCTGCGATTCTCAGGGAGCAGAGGATGTTCATGATCCA
 GACCATTGCGCAGTACAAGTTGTCTACCAAGTCCTCGCCAGTCCCTGCAGA
 ATTCCAGGCTCATTGATCTCCTCCGGATGCGAGCTCTGGAGGAGGGACGC
 AGCTCTGCTCGCAGGGGGCGGCCACTCGACAAACATCGCCTCCCCAGCC
 AGAGGGTGGATGGCTGGCAGCAGGCAGAACGCCAGAGTTACTCACAAACATCA
 TGTATTATTTATATAAGATAATITATTGGTCTTGGAAATAAGTTCTG
 TGAGTTATTATATAATGCTCCCCCCCACACACACACACAATAATAGTGCT
 TCTCATTG (SEQ ID NO:1)

FIGURE 1B

underlined = deleted in targeting construct

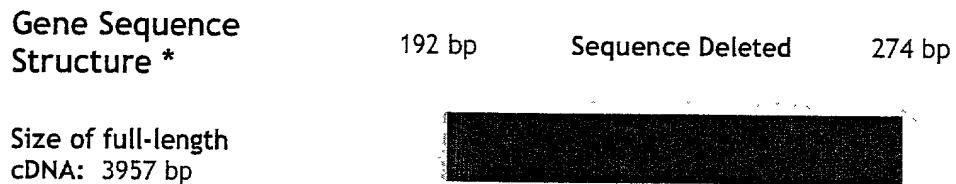
bold = sequence flanking Neo insert in targeting construct

AGCAGAGAGCCTGGTGGGCATGGACATCTTATCCACATACACTAGTGTGACCACGCCGA
CAGAAAACTACTAAGGCCATCTCAGGGGTGCTGTGCCAGGAGAGGGGGCGGTGTCCCC
GGGCCGCAGAGCCATGCCCTTCGGCCTGAAGCTCCGCAGAGGACTCGGCCTACAACGTCCT
GAGCAAGAACTGCTTGTGCCCGATCCGCTGTGACAGCATGTCATCGAGTGCAC
GCTGTCGGTGGAAAGCACGGGCAAGAGTGCTGGAGGCCAGGGTGGG
GAGGGGAGCGCACTACTTCGGCTTTGGTTCTCAGCAAGAGCCAGCAGGGAGATGGG
AGAGCTGGAGAAGCCACTGAAGAAACTCTGGACAGTTGCTAACGAGCCTCTGCTTT
CTTCGGAGTCATGTTCATGTGCCAAATGTGCACGGCTTCAGCAGGGCCAAGATA
TCAGTATTACCCTGCAAGTCAAAAAACGGTGCTGAGGGACGTGCACTTCGGGAGATTAACAGTT
TGATTCCCAAAGGTTCCTCCGGAGGATTGTGCTTTCCATGATTGGCATGGAGGA
GGCGGCTTGGGGAGGCTACCAGGGGTGCCAGGAACAAAGCTCATGCGGGAT
CCTGCCGCTGGAAGTGAAGCTGATTGACATCAACGGAGGTTGGATGGATTTGG
ACAGGAGTTTCCCCGTGAAGGACAGAGTCAGGTGCACCTCGCATTTCTT
CATGGGGATTTTGTGAGGAACAGGGTCGGGAGACAGGCGAGTGATATACAAGGTGGAATGA
CATTGGGGAGTTTACTCACAGGCAAGCCATCCTGTTGGGAGTGATTGACAAGGGGA
GACCGCGCTTCCATACACAGGAGTTATTGAAAAGTGCAAGTACATTTTCGGGTTTAC
CATCTCGGCAAAATTTACAAACAGAACAGATTGTCACTGACAGTCAAATTCTCCACC
CCCAATCAGACGCCAGCCACCTGGAGGCCCGCTCACTGCCAAGGCAGCCGTATTAT
CTTGCCCTCCCATGCATTGTCCCAGTGCAGCTACTCGGAGACCCCATACTTCCCAAGA
CAGCATTTTCCCCGGGAACGAGAAGGCTTTGTACTGCCTTCCAAACAGCCCTGACCT
TAATTACTTGAACGGACCCGTCACCAATGGCAGCGTGTGCAGCGTTCACACGTCAACTC
CCTCAGCGTCCCAGAGCTTCATTCAGGCGTCTCCAGGTTCCAACTTAGCATCCC
TGGGAGGTGACACTCATGAGGGCCGATTACACTCCCCAGGCCCACGCACCATCATCGT
GCCGTTTCACGGGCCACCCCCAGATTACGAGACGGGTCATGAGGGCAGATGAAGGGGGTTCT
GATGCACCGCAGACGCAGGCCGGTTCTGCGTAACCTAATTCAAACACCCATGC
CTATAACCAGGCCGAGGAACTGGGTACAGCCAGGCGGAGTGCGGGAGAGGGCATCCCTA
CACGGTTCCCCATGCACACACCCAGGGGTGCTACGGTCAAAAACTTGTAAGTCCGTCGTGACA
GATGAACCCCCAAATTTGTGCGATGCCTATCAGCCAGGGGCCAGTTCCCATTCTCACAC
AGTGAGGCATCCCAGACTAGCCAACACTGCAGCTCCAAGGGACACAACTATAGCAACGC
CCACATGCCAAGAAACTTATCATTCAGGCCGCCACCCCCTTACCCTGGGCCCCGTCCTGC
CACCCAGCCACCCCCAGACCCTGCCAGGCCCACCGCCACAGTCAGTGCAGGGCAGCAGCCTGA
TCTGGTTAACTCGGAAGGGTGCAGCTTCCGTAAGACCTCCAGGGGACAGTCTCACCTGT
GGTCCAATCAGTCTGCAGGGAGGGGTGAGGCAACCCCCTCACAGGCACACAGCCAATGGCGGG
CGGCGGGTGGGCACGGGTGAAAACGCCACAGCCTGGAGGGGTGATGAACGCATGGGTGAGG
CATGGAGGGGCCATGAACTGGAAGTCACTCAATATCCCATGGTCTGCCGCAAACCCCTTCG
GGAGCAGGGCCCTTCGGAGGAGGACGGGGCGGCACGGAAGTGCAGGGTCTCCCCAGTTATCA
CCACAAGAAAGACATTCTCGGATGCCACCAGTGATCCAGCAGAGTGTGAGGCGGAGGAGA

FIGURE 2A

GGAGGAGACCCTGGAGGCTGCACCTCAGGTTCTGTGCTCGAGAGAGAAAGTAGAATACAG
TGCCCAGCTGCAGGCTGCCCTGGCCCGCATCCCCAACAGGCCACCTGAGTACCCAGG
GCCAAGAAAAAGTGTCACTGAGACAGGACCAGGGAACCCCTTCCCTGC
CATGGCCAGGTGCAGGGTGTGAGACACGGACCATCCAAGGCCCTCAGTGTCTCCGGGC
AGAGCAGCTGGCTGTCAACGGTGCCTCTGGTCCCATCTGAGCCTGACACTAAC
CAGCGTAAGGAGCGGGTCAAGAAAGAGCCTGTGAAGGAAAGGCCGGTGTCAAGAGATGTT
CTCCCTGGAGGACAGCATTATAGAGAGAGAGATGATGATCAGGAATCTAGAGAACAGAA
GATGACGGGCCCGCAGGCACAGAACAGAGACCGCTGATGTTGGCAGCGCTGAATGGCTCTC
GGTGGCCCGAGTGTGGGGGGAAAGATGGTCGCCATGATGCCACCCGAGTCCCCATAGA
CGAGAGGCTCAGAGCCTGAAGAACAGCTGGAAGAGATGGAATGGTGTACAGAACATGA
GCAGATTCCAACAAAAGGCCAACGGCGTCTCAGCACCGCCACTCTGCCGTGAGAACGC
CGAGCGCAGCCGGATCCGAGAACAGTTGTCCCATATGAGGAGAACAGTGGAGCTCATCCC
GACCAAAGAAAACAACACAGGCTATATCAACGCCTCCACATCAAGGTGGTGGCG
ATCAGAAATGGCACTACATCGCCACCCAGGGCCCTTGCACATACGTGCCATGACTTCTG
GCAGATGGTGTGGAGCAGGGGGTGAATGTGATGCCATGGTCACTGCAGAGGAGGAGGG
TGGACGGACCAAAAGCCATCGATACTGGCCAAACTGGGTCCAAGCATAGTTCTGCCAC
CTACGGCAAGTTCAAGGTACCACAAAGTTCCGGACAGATTCTGGTGTATGCAACGAC
GGGCCTAAAGGTGAAGCACCTGCTGCCGGCAGGAGAGGACCGTGTGGCACTTGCAGTA
CACGGACTGGCCCCACCACGGCTGTCCAGAACAGACGTCCAAGGATTTGTCTACTTGG
GGAAATCCAGTCAGTCCGACGCCACACCAACAGCGTGTGGAAAGGCATCAGGACCAGGCA
CCCCCCCCTCGTGGTCACTGCAGCGGGTGTGGAAAGGACTGGTGTGGTTATCCTCTC
TGAGCTCATGATCTACTGCCTGGAACACAACAGAAAAGGTGGAGGTGCCACGATGCTGCG
ATTCCCTAGGGAGCAGAGGATGTTCATGATCCAGACCATTGCGCAGTACAAGTTCGTCTA
CCAAGTCCTCGTCCAGTTCTGCAGAATTCCAGGCTCATTTGATCTCCTCCGGGATGCAG
CTTCTGGAGGAGGGACGCAGCTCTGCCTGCAGGGGGCGGCCACTTCGACAACATCTGCC
TCCCCCAGCCAGAGGTGGATGGCTGGCAGCAGGCAGAACGCCAGAGTTACTCACAAACATC
ATGTATTATTTATATAAGATAATTATTTTTCCCTTTGGAATAAGTTCTGTGAGT
TATTATATAATGCTTCCCCCCCATAACACACACACAATAATAGTGTCTCATTG

FIGURE 2B

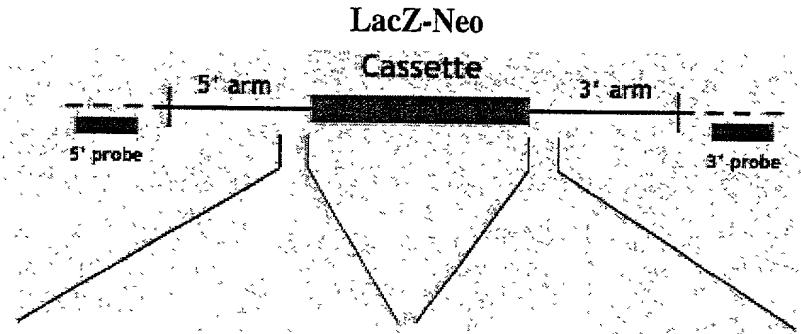
**FIGURE 3**

Targeting Vector*
(genomic sequence)

Arm Length:
5': 3.5 kb
3': 2 kb

Targeting Vector
- - - Endogenous Locus

* Not drawn to scale



```
5' >CAGCTGCCCGCAGAGAGCCT
GGGGGCATGGACATCTTATCCA
CATACCTTAGTGTGACCAACGCCGA
CAGAAAACTACTAAGGCATCTCA
GGGGTGCCTGTGCCAGGAGAGGGG
GGCGGTGTCCCCGGGCCAGAGC
CATGCCTTCGGCCTGAAGCTCCG
CAGGACTCGGCCTACAACGTCC
GAGCAAGAACT<3' (SEQ ID
NO:2)
```

```
5' >GAGGCCGTGCCAGAGGCTG
GAGCTAGGGAGGTGAGTTGAGCG
CGCATCCCTGCCCTGTTGTGGAC
AGGGAGTGGGCTTTCAGAGGAAC
CAGCTATCTGCTTAACGTGTTGGC
ACCTGCTGTGTTTCAGCCTAACG
GTGTGTTAAAAGAACCTGCTTT
CTTAGGGTGGGTGTGGCCCCGGGA
AGTTCCAGCAT<3' (SEQ ID
NO:3)
```

FIGURE 4